

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference PG3535/WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/02738	International filing date (day/month/year) 18/08/1999	Priority date (day/month/year) 19/08/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 15/02/2000	Date of completion of this report 30.11.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Nichogiannopoulou, A Telephone No. +49 89 2399 8054



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02738

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).*):

Description, pages:

1-48 as originally filed

Claims, No.:

1-8 as received on 12/10/2000 with letter of 12/10/2000

Drawings, sheets:

1/16-16/16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02738

the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:
see separate sheet

II. Priority

1. This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
 copy of the earlier application whose priority has been claimed.
 translation of the earlier application whose priority has been claimed.

2. This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.
 claims Nos. 1-5 and 7, 8.

because:

- the said international application, or the said claims Nos. 7, 8 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. 1-5 are so inadequately supported by the description that no meaningful

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02738

opinion could be formed.

- no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 6-8
	No:	Claims
Inventive step (IS)	Yes:	Claims 6-8
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 6
	No:	Claims

2. Citations and explanations see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/02738

Re Item I

Basis of the report

1. This report was established based on the application documents and the written sequence listing pages 1-23.
- 2.1. Amended claims 1-4 filed with the letter of 12.10.2000 are not allowable under Article 34(2)(b) PCT because they introduce subject-matter extending beyond the content of the application as filed. In particular, the added feature of a "pharmaceutical formulation" appears unsupported in the description of the application as originally filed. As a consequence, this report has been established as if said claims were not restricted to a pharmaceutical formulation (Rule 70.2(c) PCT).
- 2.2. The remaining amendments filed with the letter of 12.10.2000 are considered formally allowable under Article 34(2)(b) PCT because they do not introduce subject-matter extending beyond the content of the application as filed.

Re Item II

Priority

1. The present application validly claims priority from 19.08.1998. Any documents cited in the International Search Report as P documents have therefore not been considered as comprised in the prior art relevant for the present application.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/02738

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No opinion will be formulated on novelty, inventive step and industrial applicability of new claims 1-5 because said claims are found to lack disclosure and support by the description under Articles 5 and 6 PCT, to the extent that a meaningful examination cannot be performed. Although vague formulations relating to inhibitors of the binding between GRIP and CD28 are found throughout the description, no such inhibitor is being actually disclosed.

2. New claims 7 and 8 -since they concern *in vivo* methods- relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty and Inventive step (Article 33(2) and (3) PCT)

The present application discloses the identification and cloning of GRIP, a Grb2-like protein binding to phosphorylated CD28. A method of identifying an inhibitor of binding between GRIP and CD28 as well as a method for treating a patient by administrating an inhibitor have not been disclosed in the available prior art. Claims 6-8 are thus considered to fulfill the requirements of Article 33(2) and (3) PCT.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/02738

2. Industrial applicability (Article 33(4) PCT)

The subject-matter of claims for which an opinion has been established (see item III) appear to be industrially applicable thus fulfilling the requirements of Article 33(4) PCT.

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(ii) PCT, document D1 is not identified in the description and the relevant background art disclosed therein is not briefly discussed.
2. Claims 1, and 5-7 contain a reference to the Figure 5 of the drawings. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

Re Item VIII

Certain observations on the international application

1. Claims 1-5 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, i. e. the inhibition of binding, which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

ART 34 AMDT

Claims

1. A pharmaceutical formulation comprising a compound which is capable of inhibiting the binding between the polypeptide comprising the amino acid sequence shown in Figure 5 or any fragment thereof containing at least the amino acid residues encoded by nucleotide residues 151 to 459 and human CD28.
2. A formulation according to claim 1 wherein the compound is capable of inhibiting the binding of the polypeptide or fragment thereof to CD28.
3. A formulation according to claim 2 wherein the compound is capable of inhibiting the binding of the polypeptide or fragment thereof at or near phosphorylated tyrosine 173 of CD28.
4. A formulation according to any preceding claim wherein the compound is selected from an antibody, antibody derivative, peptide, phosphorylated peptides or aptamers.
5. Use of a compound which is capable of inhibiting the binding between the polypeptide comprising the amino acid sequence shown in Figure 5 and human CD28 in the manufacture of a medicament for the treatment of rheumatoid arthritis, lupus, graft versus host disease, transplant rejection, inflammatory bowel disease, multiple sclerosis, psoriasis, allergic asthma or contact dermatitis.
6. A method of identifying the compound of claim 1 or 5 which method comprises the steps of:
 - (i) providing a polypeptide having an amino acid sequence shown in Figure 5 or fragment thereof containing at least the amino acid residues encoded by a nucleotide residues 151 to 459;
 - (ii) providing a candidate compound;
 - (iii) determining whether the compound of step (ii) inhibits the binding between the polypeptide of step (i) and human CD28;
 - (iv) selecting a candidate compound which inhibits the binding in step (iii)
7. A method of treating a human patient with a disorder involving CD28 expressing cells which method comprises the step of administrating to said human a compound that inhibits the binding between the polypeptide comprising the amino acid sequence shown in Figure 5 or any fragment thereof containing at least the amino acid residues encoded by nucleotide residues 151 to 459 and human CD28.
8. A method of claim 11 wherein the disorder is an auto immune disorder or cancer.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 March 2000 (30.03.00)	To: Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE in its capacity as elected Office
International application No. PCT/GB99/02738	Applicant's or agent's file reference PG3535/PCT
International filing date (day/month/year) 18 August 1999 (18.08.99)	Priority date (day/month/year) 19 August 1998 (19.08.98)
Applicant ELLIS, Jonathan, Henry	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

15 February 2000 (15.02.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Jean-Marc Vivet Telephone No.: (41-22) 338.83.38
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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PG3535/PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/02738	International filing date (day/month/year) 18/08/1999	(Earliest) Priority Date (day/month/year) 19/08/1998
Applicant GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **4** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

GRIP, HUMAN ADAPTER PROTEIN RELATED TO THE GRB2 FAMILY MEMBER

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02738

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/47 A61K38/17 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL NUCLEOTIDE DATABASE, 'Online! EBI, Hinxton, GB Trembl, ID 04376, 1 June 1998 (1998-06-01) BURGESS, J. ET AL.: "Growth factor receptor bound-protein 2 like" retrieved from TREMBL Database accession no. 043726 XP002119673 abstract</p> <p>---</p>	1-5, 13
P, X	<p>WO 98 40482 A (INCYTE PHARMA INC ; BANDMAN OLGA (US); DIEGIDIO ANTHONY P (US)) 17 September 1998 (1998-09-17) claims 1-18</p> <p>---</p> <p>-/-</p>	1-13

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

21 October 1999

11/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

Nauche, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02738

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	QIU M, HUA S, AGRAWAL M, LI G, CAI J, CHAN E, ZHOU H, LUO Y, LIU M: "Molecular cloning and expression of human grap-2, a novel leukocyte-specific SH2- and SH3-containing" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 253, no. 2, 18 December 1998 (1998-12-18), pages 443-447, XP002119672 ORLANDO, FL US the whole document _____	1-5, 13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02738

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9840482	A 17-09-1998	US 5874224 A	AU 6692598 A	23-02-1999 29-09-1998